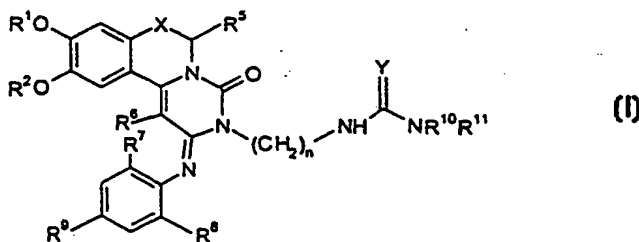




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification 7 :</b> C07D 471/04, A61K 31/519, C07D 498/04, A61K 31/553, A61P 11/00 // (C07D 471/04, 239:00, 221:00) (C07D 498/04, 267:00, 239:00)	<b>A1</b>	<b>(11) International Publication Number:</b> WO 00/58308 <b>(43) International Publication Date:</b> 5 October 2000 (05.10.00)
<b>(21) International Application Number:</b> PCT/GB00/01193 <b>(22) International Filing Date:</b> 29 March 2000 (29.03.00)  <b>(30) Priority Data:</b> 9907454.4      31 March 1999 (31.03.99)      GB 9909802.2      28 April 1999 (28.04.99)      GB  <b>(71) Applicant (for all designated States except US):</b> VANGUARD MEDICA LIMITED [GB/GB]; Chancellor Court, Surrey Research Park, Guildford, Surrey GU2 5SF (GB).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> OXFORD, Alexander, William [GB/GB]; 60 Green Drift, Royston, Hertfordshire SG8 5BX (GB). JACK, David [GB/GB]; 6 The Slype, Gustard Wood, Wheathampstead, Hertfordshire AL4 8RY (GB).  <b>(74) Agents:</b> SHEARD, Andrew, Gregory et al.; Kilburn & Strode, 20 Red Lion Street, London WC1R 4PJ (GB).	<b>(81) Designated States:</b> AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
<b>(54) Title:</b> DERIVATIVES OF PYRIMIDO[6,1-a]ISOQUINOLIN-4-ONE		



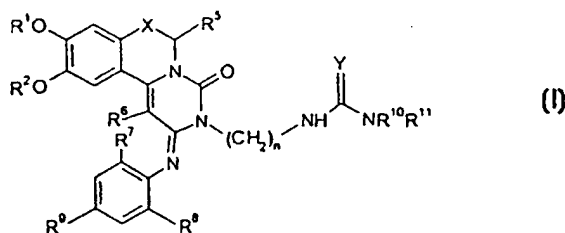
(I)

**(57) Abstract**

Compounds of general formula (I) wherein each of  $R^1$  and  $R^2$  independently represents a  $C_{1-6}$  alkyl or  $C_{2-7}$  acyl group;  $R^5$  represents a hydrogen atom or a  $C_{1-3}$  alkyl,  $C_{2-3}$  alkenyl or  $C_{2-3}$  alkynyl group;  $R^6$  represents a hydrogen atom or a  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, amino,  $C_{1-6}$  alkylamino, di( $C_{1-6}$ ) alkylamino or  $C_{2-7}$  acylamino group; each of  $R^7$  and  $R^8$  independently represents a hydrogen or halogen atom or a hydroxy, trifluoromethyl,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{2-7}$  acyl,  $C_{1-6}$  alkythio,  $C_{1-6}$  alkoxy,  $C_{3-6}$  cycloalkyl; and  $R^9$  represents a hydrogen or halogen atom or a hydroxy, trifluoromethyl,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{2-7}$  acyl,  $C_{1-6}$  alkythio,  $C_{1-6}$  alkoxy or  $C_{3-6}$  cycloalkyl group; X represents  $OCH_2$  or a group  $CR^3R^4$ , wherein each of  $R^3$  and  $R^4$  independently represents a hydrogen atom or a  $C_{1-3}$  alkyl group; each of  $R^{10}$  and  $R^{11}$  independently represents a hydrogen atom, a  $C_{1-3}$  alkyl,  $C_{3-6}$  cycloalkyl or phenyl group; y represents an oxygen atom or a group  $CHNO_2$ ,  $NCN$ ,  $NH$  or  $NNO_2$ , n is an integer from 2 to 4; or a salt thereof; are useful for treatment of respiratory disorders such as asthma. Compounds of the invention have a longer duration of action than the known compound trequinsin (9, 10-dimethoxy-3-methyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido[6,1-a]isoquinolin-4-one) and do not have trequinsin's very bitter taste.

### ABSTRACT

The invention provides compounds or salts thereof of the general formula (I):



wherein each of R<sup>1</sup> and R<sup>2</sup> independently represents a C<sub>1-6</sub> alkyl or C<sub>2-7</sub> acyl group; X represents OCH<sub>2</sub> or a group CR<sup>3</sup>R<sup>4</sup>; wherein each of R<sup>3</sup> or R<sup>4</sup> independently represents a hydrogen atom or a C<sub>1-3</sub> alkyl group; R<sup>5</sup> represents a hydrogen atom or a C<sub>1-3</sub> alkyl, C<sub>2-3</sub> alkenyl or C<sub>2-3</sub> alkynyl group; R<sup>6</sup> represents a hydrogen atom or a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub>) alkylamino or C<sub>2-7</sub> acylamino group; each of R<sup>7</sup> and R<sup>8</sup> independently represents a hydrogen or halogen atom or a hydroxy, trifluoromethyl, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>2-7</sub> acyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkoxy, C<sub>3-6</sub> cycloalkyl; and R<sup>9</sup> represents a hydrogen or halogen atom or a hydroxy, trifluoromethyl, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>2-7</sub> acyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkoxy or C<sub>3-6</sub> cycloalkyl group. The compounds or salts thereof are useful for treatment of respiratory disorders such as asthma. Compounds of the invention have a longer duration of action than the known compound trequinsin (9,10-dimethoxy-3 methyl-2-mesitylimino-2,3,6,7-tetrahydro-4H-pyrimido[6,1-a]isoquinolin-4-one).